REMARKS

Claims 1 to 7, 9 to 15, 19 and 22-27 are pending in this re-issue application. None have been allowed. Applicants note that on page 6 of this paper, claims 22-27 are underlined to indicate that in their original form, claims 22-27 were added by a Preliminary amendment filed with this re-issue application.

Applicants gratefully acknowledge that their previous amendments and arguments were determined to have overcome the previous rejections.

At the bottom of page 2 of the Office Action, the Examiner requires Applicants to comply with the sequence rules. In particular the Examiner states:

> Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants do not provide specific SEQ ID NO to the sequences depicted in the drawings either on the drawings or in the figure description. Furthermore in response to the previous reminder to comply with sequence rules by filing or requesting the transfer of the electronic form of the sequence information from the parent application to the instant re-issue application to the STIC library, applicant makes a request under the remarks section for transfer of the sequences form the parent to the instant application. However, such a request is improper and the applicant is urged to make the request on a separate sheet of paper and use the form paragraph enclosed here with as an appendix. Examiner also urges applicant to see particularly 37 CFR 1.821(d) and (e).

In response and pursuant to MPEP 2422.05, applicants have enclosed a separate paper requesting the transfer of applicants previously filed sequence information.

At the bottom of page 2 the Examiner acknowledges Applicants request that the issue of surrendering the original patent be held in abeyance until allowable subject matter is identified. Applicants respectfully request that the Examiner confirm that their request has been granted.

At the top of page 4 of the Office Action the Examiner rejects Claims 19, 26 and 26-27 under 35 USC 101 as follows:

> Claims 19, 26-27 are drawn to "a transformed host that expresses" which could read on a transformed human, a non-statutory subject matter. While applicant may argue that the word "transformed" shows the hand of man, such an argument is still not persuasive to overcome the rejection because transforming a human by itself is a non-

> statutory subject matter. Amending the claim to recite "a transformed host cell that express" which appears to be the actual intention of the applicant, would overcome the above rejection.
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> Claims 19, 26-27 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.
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> Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR. 1.173(b).

In response, applicants hereby amend the claims as suggested by the Examiner. In particular, applicants have inserted "cell" after "host" in claims 19, 26 and 27.

At the bottom of page 4 of the Office Action, the Examiner rejects Claims 1-3, 6-7, 11, 14 and 4-5, 12-13 and 15 which depend from them as indefinite under 35 USC 112, second paragraph. The Examiner states as follows:

Claims 1-3, 6-7, 11, 14 and claims 4-5, 12-13, 15 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3, 6-7, 11 and 14 are drawn to an assay for determining the COX-2 activity "of a sample" comprising the steps of adding a cell preparation, a sample comprising a COX-2 inhibitor and arachidonic acid followed by measuring the amount of PGE produced. The step (a) is highly confusing to the Examiner because it is not clear whether the "sample" in the preamble of the claims and the "sample" in step (2) of (a) are one and the same. If they are one and the same, then it is not clear to the Examiner as to how one of ordinary skill in the art can expect to test the activity of the sample having an inhibitor of the enzyme. It is not clear whether applicants meant to claim and assay to determine the COX-2 inhibitory activity of a sample, wherein said sample comprises a putative COX-2 inhibitor. On the other hand if applicant did not mean the above, Examiner request clarification.

Applicants respectfully traverse and respectfully submit that the Claims in question are correct as they stands. The "sample" mentioned in the preamble is the same as the "sample" mentioned subsequently. Those of skill in the art fully appreciate that the "putative COX-2 inhibitors" of the claims in question may be a potent inhibitor of COX-2 or a poor inhibitor of COX-2 or may be somewhere in between. It follows that COX-2 activity measured in the "sample" may indistinguishable from zero (in the case of a potent COX-2 inhibitor), may

be indistinguishable from a cell preparation having no putative inhibitor (in the case of a poor COX-2 inhibitor), or may be somewhere in between. Stated another way, the inhibitory activity is not something directly measured. It is something arrived at by calculating the difference in activity in samples with and without a putative inhibitor. See Examples 1, 2 and 5 in the instant application.

At the middle of page 5 of the Office Action the Examiner rejects Claim 14 on the basis of insufficient antecedent basis. The Examiner states:

> Claim 14 recites the limitation "a sample according to claim 10" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Applicants agree that assay claim 14 cannot depend from claim 10. Accordingly, applicants have amended claim 14 to depend from assay claim 11.

Bridging pages 5 and 6 of the Office Action, the Examiner rejects Claim 19, and 22-25 under 35 USC 112, second paragraph. The Examiner states:

Claims 19, 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 19, 22-25 all refer to sequences in figures and recites specific SEQ ID NO in parentheses. Such a depiction is confusing and unclear to the Examiner. This is because applicants do not provide a SEQ ID NO for the sequences depicted in the figure and therefore it cannot be taken for granted that the sequences in the figures and those listed in the sequence listing with appropriate SEQ ID NO are one and the same. Examiner urges applicants to refrain from referring sequences to the figure and provide only SEQ ID NO. Correction is required.

In response, applicants have deleted from the claims the reference to the Figure numbers. Applicants affirm that the sequences in the figures and the SEQ ID No's are identical.

At the bottom of page 6 of the Office Action, the Examiner rejects Claims 19 and 22-25 under 35 USC 112, first paragraph. The Examiner states:

> Claims 19, 22-25 are directed to humancycloxoygenase-2 cNDA with SEQ ID NO:11 and purified, recombinant or isolated human cyclooxygenase-2 polypeptide having an amino acid sequence SEQ ID NO:10. Claims 16-25 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from

> humans that have not been disclosed in the specification. The examiner maintains the position that the single representative disclosed species, i.e., the polypeptide with SEQ ID NO:10 and the polynucleotide with SEQ ID NO:11, fails to represent the entire genus of claimed human cyclooxygenase-2 polypeptides (underline added for emphasis).

Applicants respectfully disagree that the claims in question "are directed to a genus of polypeptides derived from humans that have not been disclosed in the specification." (emphasis in original)[1]. Claims 19 and 22-25 are limited to a single, exemplified form of human COX-2 protein as disclosed in both SEQ ID NO:10 and Figure 1A-B. These claims do not recite a genus of COX-2 proteins. Instead, claims 19 and 23-25 recite various recombinant, isolated and/or purified forms of this single, exemplified form of a human COX-2 protein; a biologically superior form of human COX-2 protein which comprises an amino acid sequence as shown in SEQ ID NO:10. Claim 19 also reads on a nucleotide sequence which encodes SEQ ID NO:10, including SEQ ID NO:11 and any alternative codon usage, as long as said codon optimized form results in expression of this single, biologically superior form of human COX-2 protein. Claim 22 reads directly on a portion of the nucleotide sequence represented by SEQ ID NO:11.

Applicants respectfully take the position that application of *Eli Lilly* and *Fiers* is misapplied to claims 19 and 22-25. *Eli Lilly*[2] stands for the proposition that disclosure of a single species of gene X (say, for example, a rat form of gene X) does not necessarily provide an adequate written description to support a claim covering identification of another mammalian form of gene X (say, a human form). In order to meet the written description requirement under *Eli Lilly*, the applicant must arguably supply the complete DNA sequence of the human form of gene X. In other words, applicant must disclose the "structure, formula or chemical name"[3] of the form of gene X which they lay claim. The requirements of *Eli Lilly* are easily met in the instant specification. This application discloses a *single* cDNA and expressed protein from a *single* species (i.e., human). In addition, Applicants supply the *complete, nucleotide sequence* for this superior form of human COX-2 (i.e., SEQ ID NO:11). Therefore, Applicants meet the *Eli Lilly* standard by disclosing both the complete nucleotide and amino acid sequence of human COX-2 as provided in SEQ ID NOs: 11 and 10, respectfully.

In contrast to the Examiner's stated position, these rejected claims do not read on "a subset of this genus of polypeptides having greater than 95% amino acid sequence identity to

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[1] Office Action at page 6, lines 20-21.
[2] *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398.
[3] Id at 1405, quoting *Fiers v. Revel*, 25 USPQ 1601 @ 1606.

SEQ ID NO:10/11 and having said activity."[4] To do so would be to arguably read on a prior art form of human COX-2 (see, the comparison with the Hla sequence in Example 5 of the instant application). Instead, claims 19 and 22-25 read on either (1) a specific form of human COX-2, depicted as SEQ ID NO:10, which represents a biologically superior form of human COX-2 over that previously known in the art; or, (2) a nucleotide sequence that encodes this specific, biologically superior form of human COX-2 (i.e., SEQ ID NO:11 or any codon optimized version thereof, as long as that nucleotide sequence encodes SEQ ID NO:10[5]). Support for claims 19 and 22-25 can found throughout the specification (e.g., see Figure 1A-B, Figure 2A-B, column 3, lines 39-47 of the original '297 patent). In view of the above discussion, Applicants respectfully take the position that this §112, first paragraph rejection of claims 19 and 22-25 is traversed. Reconsideration and withdrawal of this rejection is respectfully requested.

At the bottom of page 8 of the Office Action the Examiner rejects Claim 8 under 35 USC 103(a) over Rodan, et al. al. The Examiner states:

> Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rodan et al. (J. Bone Mineral Res. 1986, Vol. 1(2):213-220 cited in Form 1449). Claim 8 in this instant application is drawn to a composition comprising an osteosarcoma cell preparation or 50-500 micro gram of osteosarcoma microsomes and 01. to 50 micro liters of arachidonic acid per c.c. of cell preparation.
>
> Rodan et al. teach several types of human osteosarcoma cell and provide cell culture composition of the same. The reference also teaches the use of said cells for assay of COX activity along with exogenous use of arachidonic acid in such reactions. Rodan et al. actually investigate the basis for differences in prostaglandin synthesis among osteosarcoma cell lines and examine the effect of a number of bone resorbing agents on prostaglandin production and report that the differences in PGE synthesis between osteoblastic and non-osteoblastic rat osteosarcoma cells were associated with COX dependent release of arachidonic acid.
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> With the above teaching of Rodan et al. in hand, it would have been obvious to those skilled in the art to make several types of cell preparation to study the above aspects, one of which would be a cell preparation between 103 or 105 or 109 (as required) osteosarcoma cells per c.c. along with varying amounts of arachidonic acid such as 01 to 50 or 100 micro liters. One of ordinary skill in the art would have been

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[4] Office Action at page 7, lines 16-18

> motivated to do so in order to set up reactions to study the effects of bone resorbing agents on PGE synethesis. One of ordinary skill in the art would have a reasonable expectation of success since Rodan et al. provide the cells and a detailed information regarding their role and their physiology.

While applicants make no admissions with regard to this rejection, applicants have canceled claim 8 in order to advance the prosecution of this application. Applicants specifically reserve the right to prosecute the unclaimed subject matter in a continuing or divisional application. Consistent with canceling claim 8, applicants have amended claim 9 (which was previously dependent on claim 8). In particular, applicants have converted claim 9 into independent claim form. This amendment is supported by original claims 8 and 9 and, as such, adds no new matter.

Having addressed all of the outstanding objections and rejections, applicants respectfully submit that the application is now in condition for allowance and passage thereto is earnestly requested. The Examiner is invited to contact the attorney at the telephone number provided below, if such would advance the prosecution of this case.

Respectfully submitted,

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Marked up copies of the presently amended claims is as follows, wherein an underline denotes language added and brackets denote language deleted:

Claim 9. (Once amended) A composition [according to claim 8] comprising:

(a) an osteosarcoma cell preparation having $8x10^4$ to $2x10^6$ osteosarcoma 143.98.2 whole cells per cc of cell preparation or 100 to 400 µg of osteosarcoma 143.98.2 microsomes; and 10 to 20 µl of peroxide-free arachidonic acid per cc of cell preparation; and

(b) 0.1 to 50 µl of arachidonic acid per cc of cell preparation.

Claim 14. (Once amended) An assay according to claim 11 for determining the cyclooxygenase-1 activity of a sample [according to claim 10] comprising the steps of:

(a) adding

(1) a COX-1 cell preparation,

(2) a sample, said sample comprising a putative cyclooxygenase-1 inhibitor;

(3) arachidonic acid; and

(b) determining the amount of prostaglandin E_2 produced in step (a),

wherein the cell preparation comprises 10^5 to 10^8 whole cells of U-937 per cc, or 1 to 10 mg of U-937 microsomes per ml of preparation; and

0.1 to 50 µl of arachidonic acid per ml of preparation.

Claim 19. (Twice Amended) A transformed host cell that expresses cyclooxygenase-2 as shown in [FIG. 1 (]SEQ. ID. NO: 10[)] comprising:

(a) a mammalian or eukaryotic expression vector; and

(b) a sequence encoding human cyclooxygenase-2 comprising bases 97 to 1909 as shown in [FIG. 2 (]SEQ. ID. NO: 11[)] or encodes protein of [FIG. 1 (]SEQ. ID. NO: 10[)].

Claim 22. (Twice amended) Human cyclooxygenase-2 cDNA comprising the coding region which is bases 97 to 1909 of [Fig. 2 (]SEQ. ID. NO: 11[)].

Claim 23. (Twice amended) Recombinant human cyclooxygenase-2 which is shown in [Fig. 1 (]SEQ. ID. NO: 10[)].

Claim 24. (Twice amended) An isolated human cyclooxygenase-2 which is shown in [Fig. 1 (]SEQ. ID. NO: 10[)].

Claim 25. (Twice amended) Purified human cyclooxygenase-2 which is shown in [Fig. 1 (]SEQ. ID. NO: 10[)].

Claim 26. (Once amended) The transformed host cell according to claim 19 wherein the expression vector is a vacinia or baculovirus vector.

Claim 27. (Twice amended) The transformed host cell according to claim 19 wherein the cyclooxygenase-2 is expressed in COS-7 cells.